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ORIGINAL ARTICLE

Serum procalcitonin and high sensitivity C-reactive protein in distinguishing ADHF and CAP

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KEYWORDS

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Abstract *Background:* Rapid and accurate diagnosis and management can be lifesaving for patients with acute dyspnea. However, making a differential diagnosis and selecting early treatment for patients with acute dyspnea in the emergency setting are a clinical challenge that requires complex decision-making in order to achieve hemodynamic balance, decrease unnecessary usage of antibiotic therapy, and decrease mortality.

Aim: To study the efficacy of measuring high sensitivity C-reactive protein (Hs-CRP) and procalcitonin (PCT) levels on admission in differentiating acute decompensated heart failure (ADHF) from community acquired pneumonia (CAP) in patients with acute dyspnea in the emergency setting.

Methods: A comparative analytical study of ADHF included CAP patients admitted to the emergency room for acute dyspnea. Patients who qualified the criteria for both pneumonia and heart failure were excluded. Efficacy for Hs-CRP and PCT as a diagnostic markers was evaluated by using receiver operator curves (ROC).

Results: Thirty patients with ADHF and 30 patients with CAP were studied. Patients with pneumonia had increased Hs-CRP and PCT levels on admission (mean values were 76.6 ± 41.8 mg/L, and 0.95 ± 0.54 ng/ml, respectively), compared with those with heart failure (18.53 ± 18.49 mg/L, and 0.09 ± 0.03 ng/ml, respectively). For differentiating pneumonia from HF, the cutoff value of Hs-CRP was 15 mg/L, with sensitivity 96.7% and specificity 70%, while the cutoff value of PCT was 0.2 ng/ml with sensitivity 93.3% and specificity 100%.

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Conclusion: Procalcitonin and Hs-CRP levels can both independently distinguish CAP from ADHF in the emergency setting.

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Introduction

Acute dyspnea is one of the most common causes of emergency department (ED) admission. It is also the main symptom for which patients with acute decompensated heart failure (ADHF) require treatment. The early evaluation of acute shortness of breath poses a diagnostic challenge for the physician, and the timely differentiation from potential causes of dyspnea may permit the implementation of appropriate medical therapy.

ADHF has emerged as a major public health problem over the past 2 decades [1]. Heart failure is the leading cause of hospitalization in patients older than 65 years of age. HF resulting in hospitalization represents a significant and growing health care burden. In-hospital mortality is excessive and readmission is disturbingly common, despite advances in pharmacotherapy and device therapy for HF [2,3].

Suspected community-acquired pneumonia (CAP) is defined as an acute illness with cough and at least one of new focal chest signs, fever more than 4 days or dyspnea/tachypnea, and without other obvious causes [4].

Definite community-acquired pneumonia (CAP) is the same but supported by chest radiograph findings of lung shadowing that is likely to be new [4].

Differentiating the cause of shortness of breath in patients with cardiac and pulmonary diseases is a big dilemma as many of these patients present with dyspnea, mild fever and leukocytosis and upon auscultation, there are evident crackles, so history and physical examination are poor to differentiate. An accurate diagnosis of ADHF is difficult, especially in elderly or obese patients given the frequency of comorbidities such as asthma, chronic obstructive pulmonary disease (COPD), anemia, acidosis, and neurologic disorders with a lack of specificity or sensitivity to the signs and symptoms of heart failure [5].

Electrocardiographic changes are non-specific to diagnose decompensated heart failure. Chest radiograph is also non-specific as bedside films cannot assess cardiac size and the interpretation of chest roentgenograms is variable, even among radiologists [6,7].

Echocardiography is the gold standard method for detecting left ventricular dysfunction, but it is not often usually available in emergency care and its performance or interpretation requires great skill and knowledge by the operator [8].

All these can either mask or mimic a concomitant pneumonia. An erroneous diagnosis of pneumonia can generate several undesirable results in treatment, diagnostic workout, iatrogenic complications, prognosis, and misuse of health resources [9,10].

The identification of biomarkers such as procalcitonin (PCT) and High sensitivity C-reactive protein (Hs-CRP) for the early presentation can guide treatment, reduce misuse of antibiotics and possibly improve long term outcomes.

C-reactive protein (CRP) is a pentameric protein comprised of five identical units. Several functions have been attributed to C-reactive protein: CRP is capable of binding various biological substrates; it participates in the activation of the complement system and modulates the function of phagocytic

leukocytes. CRP is also located at sites of inflammation; it enhances macrophage action on tumors; it is implicated in the synthesis of interleukine-1 (IL-1) and tumor necrosis factor (TNF), and is capable of binding and blocking platelet activating factor. CRP is mainly produced in the liver in response to interleukine-6 (IL-6) [11,12].

Elevated levels of CRP have been observed in patients with heart failure, and activation of the immune response may play a role in heart failure through modifications in the renin-angiotensin-aldosterone system (RAAS) and sympathetic system [13]. It is also found that higher CRP levels are related to progressive myocardial functional deterioration independent of subclinical atherosclerosis and clinical coronary events in asymptomatic individuals without previous history of heart disease [14].

Procalcitonin is 116 amino acid prohormone of the hormone calcitonin. Calcitonin is exclusively produced by c-cells of the thyroid gland in response to hormonal stimuli, whereas procalcitonin can be produced by several other cell types from a wide range of organs in response to inflammation or infection [15].

Plasma procalcitonin has a half life of 25–30 h. Levels typically increase within 3–6 h of the stimulus and higher levels are associated with poorer prognosis. Elevated values are highly suggestive of an infection, typically bacteria, with a systemic response (sepsis, or severe sepsis or septic shock) [16,17].

Aim of the study

1. To determine the usefulness of serum procalcitonin and Hs C-reactive protein to differentiate patients with community acquired pneumonia from acute decompensated heart failure.
2. To identify the values of procalcitonin and Hs C-reactive protein above which we can diagnose community acquired pneumonia.

Patients and methods

We initially recruited 76 patients admitted to ED at Cairo university hospital with shortness of breath between June 2010 and June 2012. During the study, patients who qualified the criteria for both pneumonia and heart failure were excluded from the analysis because including these patients would have distorted the cutoff values for the diagnosis of either condition alone.

So this study enrolled 60 patients admitted to ED with acute dyspnea including acute decompensated heart failure and community acquired pneumonia.

Inclusion criteria

1. Patients with acute respiratory distress within 1 week.
2. Patients with or without underlying history of heart or lung disease.

Exclusion criteria

1. Patients with evidence of myocardial infarction within 2 weeks.
2. Patients with chronic inflammatory disease such as those with arthritis, because of the impact of the inflammatory conditions on the level of the CRP.
3. Women on hormone replacement therapy have been shown to have elevated Hs-CRP levels.
4. Patients with systemic steroid treatment, and anti-inflammatory drugs, because they reduce Hs-CRP in blood as they help to reduce the inflammation.
5. Pregnant women have been shown to have elevated Hs-CRP levels.
6. Patients with cardiogenic shock because it causes a pyrexia of unknown origin in patients surviving for 12 h and that is associated with a rise in procalcitonin levels [18].

*These patients were classified according to their diagnosis into two groups:

Group (A): Includes 30 cases with acute decompensated heart failure based on the Framingham criteria in which the diagnosis of heart failure requires the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria [19].

Group (B): Includes 30 cases with definite community acquired pneumonia [4].

All patients were subjected to:

1. History taking.
2. Clinical examination.
3. Chest radiograph: for assessment of cardiac size and identification of alveolar and interstitial infiltration.

Echocardiography study

Standard transthoracic M-mode, two dimensional echocardiograms were obtained to assess:

A. LV systolic function: which required

1. Left ventricular end diastolic diameter (LVED): which was measured from the leading edge of left septal surface to the leading interface of the left ventricular (LV) endocardium.
2. Left ventricular end systolic diameter (LVES): which was measured at the peak downward motion of inter ventricular septum to upward motion of the posterior left ventricular wall.
3. Diastolic function: diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole. Pulsed wave Doppler of trans-mitral flow was used to assess global diastolic function (sample volume placed at tip of mitral leaflet in the apical 4 chamber view), and measure E-wave velocity (E), A wave velocity, E-wave deceleration time and E/A ratio [20].
4. Ejection fraction (EF%) was calculated from modified Simpson method. The LV endocardial border is traced from one apical or two orthogonal apical views to create multiple (usually 20) cylinders whose volume is summated to provide LV volume and ejection fraction [21].

B. For measurement of pulmonary artery systolic pressure (PASP), applying the modified Bernoulli equation using Right

Ventricular Systolic Pressure which was estimated by measuring the peak Tricuspid Regurgitation jet velocity by Continuous Wave Doppler [22].

General laboratory investigations:

Total leukocytic count (TLC).
Erythrocyte sedimentation rate (ESR).
Sputum culture and sensitivity.

Specific laboratory investigations:

- Serum Hs-CRP level.
- Serum PCT level.

High sensitivity enzyme immunoassay for the quantitative determination of C-reactive protein concentration in human serum

Principle of the assay

The principle of a solid phase enzyme-linked immunosorbent assay (ELISA) of Hs-CRP is based on that CRP molecules in the sample are sandwiched between two antibodies. The concentration of CRP is directly proportional the color intensity of the test sample.

Assay procedure

1. Serum samples were frozen at -20°C , then they were centrifuged and diluted 100 fold prior to use.
2. Undiluted CRP standards, diluted specimens and diluted controls were dispensed into appropriate wells to be incubated and washed every step after addition of CRP Enzyme Conjugate Reagent and tetramethylbenzidine (TMB) reagent.
3. The reaction was stopped by adding stop solution and the absorbance was read after the change of the color from blue to yellow.

Human procalcitonin, PCT ELISA kit

Test principle

Procalcitonin present in the sample is bound to the immobilized antibody specific for it. The color develops in proportion to the amount of procalcitonin bound after the addition of the TMB reagent. The intensity of the color is measured after the change of the color from blue to yellow by the stop solution.

Assay procedure

1. Standard and sample were added into the appropriate wells to be incubated and washed every step after addition of biotinylated antibody, Streptavidin solution, and TMB reagent.
2. The reaction was stopped by adding stop solution and the absorbance was read.

Statistical analysis

The obtained data of every patient were collected in a separate patient sheet then tabulated in a master table and fed to the computer on SPSS version 17, statistical program for analysis of data.

Mean and Standard deviation described quantitative data. Parametric and non-parametric *t* test compared means of independent groups.

Chi-square and/fisher exact were used to test proportion independence.

ROC receiver operator characteristic curve was used to select a cut-off point for procalcitonin and Hs-CRP.

Validity measures were sensitivity and specificity.

Correlations between variables were tested by the Pearson rank correlation test (r = correlation coefficient).

p Value was considered significant ≤ 0.05 .

Results

The current comparative analytical study included 60 patients admitted to ED with shortness of breath; 30 patients with heart failure (group A) and 30 patients with community acquired pneumonia (group B). (Tables 1–7)

Comparison between the two study groups as regards diastolic dysfunction

All patients (100%) in group A had diastolic dysfunction, while 18 patients (60%) in group B had diastolic dysfunction, with statistically significant p value ($p \leq 0.001$). (Table 8)

Comparison of PCT and Hs-CRP according to the sputum culture

Twenty patients (33.3%) had positive sputum cultures in both groups: *Klebsiella*, $n = 7$ (11.7%); *Streptococcus pneumoniae*, $n = 3$ (5%); *Staphylococcus aureus*, $n = 2$ (3.3%); *Candida*, $n = 3$ (5%); MRSA, $n = 1$ (1.7%); *Klebsiella* + *S. aureus*, $n = 1$ (1.7%); *Klebsiella* + *Escherichia coli*, $n = 1$ (1.7%); *Klebsiella* + *Acinetobacter*, $n = 2$ (3.3%).

Patients with positive sputum cultures had higher levels of PCT and Hs-CRP, with statistically significant p value ($p = 0.000$). (Table 9)

Correlations between Hs-CRP level and age, NYHA (New York Heart Association) class, EF%, and PCT level in group A

- There was a positive correlation between Hs-CRP level and NYHA class ($r = 0.67$), ($p = 0.000$).
- There was a negative correlation between Hs-CRP level and EF% ($r = -0.92$), ($p = 0.000$).
- There was a negative correlation between NYHA class and EF% ($r = -0.77$), ($p = 0.000$).

Table 1 Comparison between the mean ages of the two groups.

	HF		CAP		p Value
	Mean	\pm SD	Mean	\pm SD	
Age	63.6	± 7.8	54.1	± 17.9	0.01*

* $P < 0.01$ significant.

Table 2 Gender distribution in the studied groups.

	HF		CAP		p Value
	Number	%	Number	%	
Male	17	56.70	18	60	0.79
Female	13	43.30	12	40	

Table 3 Smoking distribution in the two groups.

	HF		CAP		p Value
	Number	%	Number	%	
Smoking	11	36.70	14	47	0.43

Table 4 Comparison between the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the two study groups.

	HF		CAP		p Value
	Mean	\pm SD	Mean	\pm SD	
SBP	148.5	± 21.6	131.5	± 15.4	0.001*
DBP	97	± 9.8	87.2	± 10.2	<0.001*

* $P < 0.01$ significant.

- There was no correlation between Hs-CRP level and PCT level ($r = -0.003$), ($p = 0.98$).
- There was no correlation between Hs-CRP level and age ($r = -0.22$), ($p = 0.23$).

Correlations between Hs-CRP level and age, EF%, and PCT level in group B

- There was a positive correlation between Hs-CRP level and PCT level ($r = 0.64$), ($p = 0.000$). (Fig 1)
- There was no correlation between Hs-CRP level and EF% ($r = 0.27$), ($p = 0.15$).
- There was no correlation between Hs-CRP level and age ($r = -0.00$), ($p = 0.99$).

Sensitivity and specificity of procalcitonin to discriminate HF from CAP (fig. 2)

PCT can be used to diagnose acutely dyspnic patients with heart failure or Community acquired pneumonia: a PCT > 0.2 ng/ml defined community-acquired pneumonia and a PCT < 0.2 ng/mL defined heart failure with sensitivity 93.3% and specificity 100%. (Table 10)

Sensitivity and specificity of Hs-CRP to discriminate HF from CAP (Fig. 3)

Hs-CRP can be used to diagnose acutely dyspnic patients with heart failure or Community acquired pneumonia: a Hs-CRP

Table 5 Comparison between group A and group B as regards Fever, PND, Cough, Dyspnea, APE (acute pulmonary edema), Pulmonary rales, Raised JVP(jugular venous pressure), S3, Hepatomegaly, Hepatojugular reflux, L.L.(lower limb) edema, Weight loss, History of chest infection, and Statin use.

	HF		CAP		<i>p</i> Value
	Number	%	Number	%	
Fever	3	10	26	86.7	<0.001*
P.N.D.	24	80	0	0	<0.001*
Cough	5	16.7	19	63.3	<0.001*
Dyspnea	30	100	30	100	N.S.
APE	17	56.7	0	0	<0.001*
Pulmonary rales	27	90	22	73	0.3
Raised JVP	25	83.3	1	3.3	<0.001*
S3	12	40	0	0	<0.001*
Hepatomegaly	24	80	6	20	<0.001*
Hepatojugular reflux	6	20	0	0	0.01*
L.L.edema	22	73.3	2	6.7	<0.001*
Weight loss	7	23.3	0	0	0.005*
History of chest infection	1	3.3	26	86.7	<0.001*
Statin use	14	46.7	11	36.7	0.43

* *P* < 0.01 significant.**Table 6** Comparison of radiologic parameters in both study groups.

	HF		CAP		<i>p</i> Value
	Number	%	Number	%	
Cardiomegaly	23	76.7	4	13.3	<0.001*
Lung congestion	24	80	0	0	<0.001*
Lung infiltrate	6	20	26	86.7	<0.001*
Pleural effusion	10	33.3	6	20	<0.001*

* *P* < 0.01 significant.**Table 7** Comparison of PCT, Hs-CRP, ESR and TLC in both study groups.

	HF		CAP		<i>p</i> Value
	Mean	±SD	Mean	±SD	
PCT (ng/ml)	0.09	±0.03	0.95	±0.54	<0.001*
Hs-CRP (mg/L)	18.53	±18.49	76.6	±41.8	<0.001*
ESR	23.17	±7.63	67.77	±15.9	<0.001*
TLC (/cm)	7.93	±2.93	17.9	±5.22	<0.001*

* *P* < 0.01 significant.**Table 8** Comparison of Echocardiographic parameters in both groups.

	HF		CAP		<i>p</i> Value
	Mean	±SD	Mean	±SD	
LVED	6.09	±0.63	5.37	±0.38	<0.001*
LVES	4.97	±0.74	3.54	±0.33	<0.001*
EF	37.13	±10.89	67.77	±5.16	<0.001*
PASP	38.7	±11.85	28.50	±12.71	0.002*

* *P* < 0.01 significant.

≥15 mg/L defined community-acquired pneumonia and a Hs-CRP <15 mg/L defined heart failure with sensitivity 96.7% and specificity 70%. (Table 11)

Discussion

Heart failure and community acquired pneumonia are major health problems in developed countries and are responsible for a great number of hospitalizations and deaths.

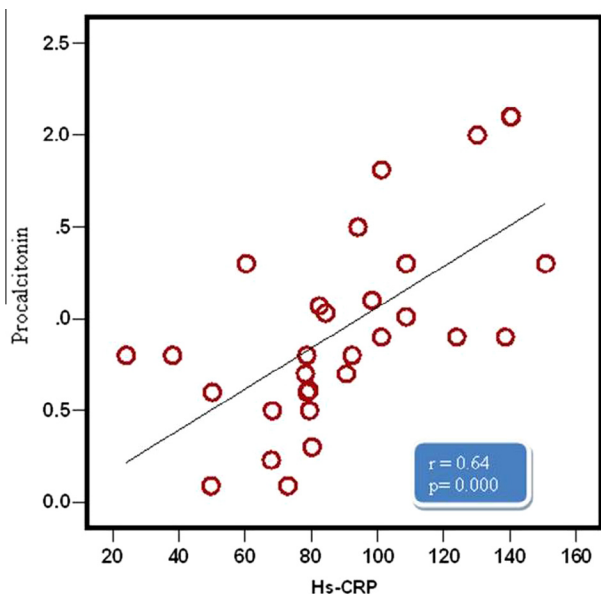
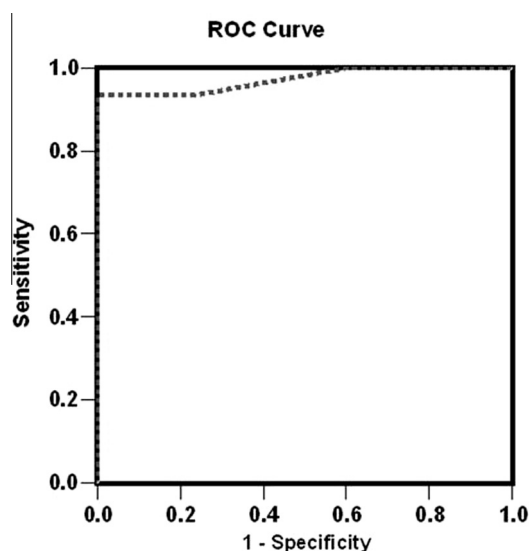
Differentiating the diagnosis of pneumonia from that of HF in patients presenting with a chief complaint of dyspnea can be difficult, and disastrous consequences may occur from a mistake [23,24] because of the similar and therefore non-specific physical exam and chest X-ray abnormalities. It is our impression that due to the difficulty of establishing a diagnosis based on clinical and radiological findings alone and due to the grave consequences of failing to diagnose these patients, misuse of antibiotics which in turn is associated with adverse reactions, high cost and the emergence of bacterial resistance [25], another criteria must be used. In this study, we evaluated serum Hs-CRP and PCT as an aid for the diagnosis of these patients.

C-reactive protein is a sensitive marker for pneumonia, it is an acute-phase protein synthesized by the liver that is found only in trace amounts in the plasma of healthy subjects. A rise in IL-6 after a tissue injury mediates the production of CRP within hours [26]. Thus, an elevated serum concentration of CRP is unequivocal evidence of active tissue damage. An increased CRP level has also been reported to be an independent predictor of heart failure in study of a community-based elderly population [27]. It is also found that higher CRP levels are related to progressive myocardial functional deterioration.

Procalcitonin has recently emerged as a promising alternative inflammatory biomarker. PCT is a peptide precursor of the hormone calcitonin and rises in response to inflammatory stimulus. It has been proposed as a marker of bacterial infection in ill patients. Use of this marker panel may improve the diagnostic accuracy over standard clinical judgment of ED physicians.

Table 9 Comparison of PCT and Hs-CRP according to the sputum culture.

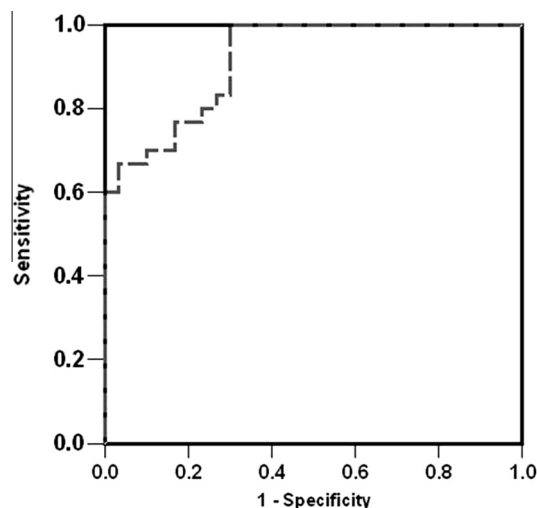
	Positive sputum culture		Negative sputum culture		<i>p</i> Value
	Mean	±SD	Mean	±SD	
PCT (ng/ml)	1.17	±0.49	0.19	±0.24	0.000*
Hs-CRP (mg/L)	87.54	±42.43	27.57	±27.31	0.000*

* *P* < 0.01 significant.**Figure 1** Correlation between Hs-CRP level (mg/L) and procalcitonin level (ng/ml) in group B.**Figure 2** ROC (receiver operator characteristic curve) of sensitivity and specificity of Procalcitonin.

In this study, we have found ADHF and Pneumonia to differ substantially in the observed levels of Hs-CRP (18.53 ± 18.49 vs. 76.6 ± 41.8 mg/L, $p < 0.001$). Employing

Table 10 Sensitivity and specificity of Procalcitonin to discriminate HF from CAP.

Procalcitonin	HF		CAP	
	Number	%	Number	%
≤0.21	30	100.00	2	7
>0.21	0	0.00	28	93.3

**Figure 3** ROC Curve of sensitivity and specificity of Hs-CRP.**Table 11** Sensitivity and specificity of H-s CRP to discriminate HF from CAP.

Hs-CRP	HF		CAP	
	Number	%	Number	%
<15	21	70	1	3.3
≥15	9	30	29	96.7

an ROC diagram, the admission level of hs-CRP 15 mg/L was the cutoff value for ruling-in pneumonia with sensitivity 96.7% and specificity 70%.

The same was reported by Castro-Guardiola et al. who studied 284 consecutive patients diagnosed in the emergency ward as having CAP where the diagnosis was reviewed by the investigators applying pre-set diagnostic criteria. Statistical analysis was then performed comparing data from patients with a definitive diagnosis of CAP (208 patients) with those with a final diagnosis of non-pneumonia disease (76 patients) to suggest higher cutoff value to be 100 mg/L with sensitivity 70% and specificity 96% [28].

Also, a similar study by Erel Joffe et al. as 72 patients with ADHF and 50 patients with pneumonia were included in this study. The mean CRP levels on admission were 13.5 ± 13.5 mg/L for the ADHF patients and 127 ± 84 mg/L for the pneumonia patients ($p < 0.001$), suggested the cutoff value for ruling-in pneumonia to be 72.5 mg/L [29].

The difference of the cutoff values across different studies could be explained by the use of different reagents used to measure CRP e.g. the immunoturbidimetric assay, and automated latex-enhanced turbidimetric assay.

In the present study we found that patients with HF who had higher serum level of Hs-CRP, had a higher NYHA functional class ($r = 0.67$) ($p = 0.000$). It was also proved by Alonso-Martinez et al. who studied the relation between 76 patients with heart failure and CRP (mean 3.9 ± 5.9) by using Nephelometer analyzer and stated that an inflammatory response is present in deteriorating heart failure and observed that higher CRP levels in patients with higher NYHA functional class, perhaps signaling a poor therapeutic response and higher CRP levels were also related to higher rates of readmission and mortality and it could be an independent marker of improvement and readmission in heart failure [12].

We observed that the higher the serum level of CRP, the lower the LVEF ($r = -0.92$) ($p = 0.000$). Arroyo-Espliguero et al. studied 841 patients with chronic stable angina undergoing coronary angiography and the symptoms of CHF were assessed using NYHA functional classification. CRP measurements were performed using a high sensitivity immunoassay at the time of diagnostic coronary angiography and found that Hs-CRP serum concentrations showed an inverse correlation with LVEF ($r = -0.11$; $p = 0.004$) and were an independent predictor of NYHA functional class in patients with chronic stable angina [30].

Our results suggest that PCT provides additive diagnostic information in patients presenting with shortness of breath; models using PCT were robust when clinical uncertainty existed. We found the cutoff value for ruling-in pneumonia to be 0.2 ng/ml with sensitivity 93.3% and specificity 100%, while a similar study by Cinar et al. suggested the cutoff value for ruling-in pneumonia to be 0.25 ng/ml to indicate an infectious etiology of dyspnea. He enrolled 154 patients with a chief complaint of shortness of breath and uncertain diagnosis in his study to find that PCT had 48.8% sensitivity and a 96.5% specificity with cutoff value 0.25 ng/ml [31].

Also, Maisel et al. studied 1641 patients presented to EDs with dyspnea in which 155 patients had a diagnosis of pneumonia with the median PCT concentration was 0.18 ng/ml, and for the patients without pneumonia PCT was 0.07 ng/ml [32].

Our results also found that patients with positive sputum cultures had higher levels of PCT and hs-CRP compared to patients with negative sputum cultures, with statistically significant p value ($p = 0.000$).

Also, Schuetz et al. found a high diagnostic performance of PCT with a cutoff of 0.25 ng/ml to exclude bacteremic disease in patients with CAP, and also found that PCT demonstrated a better discriminatory ability compared to white blood cells and CRP to distinguish blood contamination from true blood stream infection in patients with growth of coagulase-negative staphylococci in their blood cultures with a cut-off value of 0.1 ng/ml [33].

Conclusion

This study assessed the efficacy of measuring Hs-CRP and procalcitonin levels on admission in differentiating ADHF from CAP in patients with acute dyspnea in the emergency setting.

Our findings indicate that patients with pneumonia had increased Hs-CRP and PCT levels on admission compared with those with heart failure.

The cutoff value for Hs-CRP for differentiating pneumonia from HF is 15 mg/L.

The cutoff value for procalcitonin for differentiating pneumonia from HF is 0.2 ng/ml.

Our findings indicate that the levels of Hs-CRP increase with the severity of CHF, as we observed that the higher the serum level of Hs-CRP, the higher NYHA functional class and the lower LVEF.

According to our findings, Hs-CRP and procalcitonin measurements may be used since the first day of hospitalization for differentiating community acquired pneumonia patients from acute decompensated heart failure patients.

Conflict of interest

None.

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